The instant amendment relevant to the subunit antigen of the invention requires only a cursory review by the Examiner. The particular *E. coli* O157:H7 antigens prepared from the O-specific polysaccharide of *E. coli* O157:H7 being used in the claimed method are described in the application on page 5, lines 3-4 and in the Information Disclosure Statement citation WO 00/04922 that had been reviewed by the Examiner and made of record on February 25, 2005. Therefore, the claims, if amended as proposed, do not present any new issues requiring further search.

Under the guidelines of M.P.E.P. § 714.13, any refusal to enter the proposed amendment should not be arbitrary. The proposed amendment should be given sufficient consideration to determine whether the claims are in condition for allowance or whether the issues on appeal are simplified. Applicants hope that the Examiner will enter the amendment, reconsider the rejections of record and allow the pending claims.

In accord with 37 C.F.R. § 1.121, the proposed amendment to the claims and a complete listing of all claims begin on a separate sheet. As required, only the claim number and status indicate the canceled claims. For the convenience of the Office staff, the amendment is placed in the below Appendix and incorporated herein by reference thereto. The amendment adds no new matter. Support for the amendment inserting "an antigen prepared from an O-specific polysaccharide of *E. coli* O157:H7" in lieu of the term *subunit* is found on page 5, lines 3-4 of the specification. Support for indicating that the vaccine is being administered to animals is found on page 7, lines 14-20 of the specification and elsewhere.

Turning to the Office action at hand, the Examiner made the restriction requirement final and withdrew non-elected Claims 1-19 from consideration. Applicants are canceling the non-elected claims without prejudice to filing a divisional application in due course.

Applicants are grateful that the Examiner kindly withdrew the objection to the specification, the objection to Claim 21 and the rejection of Claims 20-21 under 35 U.S.C. § 112, first paragraph.

The Examiner has maintained the rejection of Claim 20 (now rewritten Claim 22) under 35 U.S.C. § 102(b) as being anticipated by Finlay *et al.* for reasons of record explained on pages 4 and 5 of the current Office action.

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In view of the present amendment, Applicants' response overcomes the outstanding rejection. Specifically, the holding of anticipation cannot be sustained because any inference of an identity of invention between Applicants' claimed invention and the cited reference of Finlay *et al.* no longer exists. The amendment ensures that the claimed invention is not identically described in the reference to any extent.

Finlay *et al.* only describe compositions that employ the EHEC cell culture supernatant ("CCS") derived from an *E. coli* culture with or without supplementation of additional EHEC secreted proteins such as Esp A, Esp B, Esp D, Tir and Intimin. Finlay *et al.* define their EHEC cell culture supernatant explicitly as a supernatant that is substantially free of EHEC bacterial cells or the lysate of such cells [0055]. In the process of making the concentrated supernatant, the whole cells are removed by centrifugation [0107]. In no uncertain terms, Finlay *et al.* do not describe the use of any bacterial vaccine, let alone Applicants' novel inactivated or killed whole *E. coli* bacterin as a vaccine for reducing the shedding of *E. coli* O157:H7.

In terms of the subunit component, the Examiner asserts that Finlay *et al.* disclose the use of immunogenic fragments, which the Examiner views as a "subunit" of *E. coli* O157:H7. These immunogenic fragments are disclosed in the reference as fragments of about 3 or more amino acids of the parent EHEC secreted protein molecule. However, the fragments do not possess the antigenic determinant by themselves. Finlay *et al.* do not even suggest using their immunogenic fragments as subunit vaccines or administering the fragments in the absence of the EHEC CCS. In point of fact, based on the examples and claims of Finlay *et al.*, the immunogenic fragments cannot induce sufficient immunity to protect against an infection of *E. coli* O157:H7. Therefore, the immunogenic fragments of Finlay *et al.* would not demonstrate adequate antigenic activity to imply any utility as a subunit vaccine of *E. coli* O157:H7.

Besides, such immunogenic fragments that require the co-presence of the EHEC CCS for protective activity are not employed in the present invention. Without any doubt, Applicants' antigen of *E. coli* O157:H7 as now claimed is not the same entity as the composition comprising the immunogenic fragments in combination with the EHEC CCS that was described by Finlay *et al.* It is quite clear that the particular antigen of the present invention taught in the instant application, namely, an antigen prepared from an O-specific polysaccharide of *E. coli* O157:H7, is not described or proposed in the reference of Finlay *et al.*

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Since Applicants' vaccine composition and method of use thereof are not identically disclosed in the reference, the present invention is not anticipated by the art.

In view of the present amendment, it is respectfully asked that the rejection of Claim 22 under 35 U.S.C. § 102(b) be withdrawn.

The Examiner also continues to reject Claim 21 (now rewritten Claim 23) under 35 U.S.C. § 103(a) as being unpatentable over Finlay *et al.* in view of Brashears *et al.* for reasons of record set forth on pages 5-7 of the current Office action. Applicants respectfully traverse the rejection for the following reasons.

To establish a *prima facie* case of obviousness, the guidelines of M.P.E.P. § 706.02(j) and case law provide three basic criteria: (1) There must be some suggestion or motivation to modify the reference or to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the combined references must teach or suggest all claim limitations. The guidelines of M.P.E.P. § 716.02(a) further indicate that a *prima facie* case of obviousness can be rebutted by evidence of results that are unexpected and significant.

Contrary to the Examiner's contention, Applicants have not argued the references individually. Instead, Applicants' sound position is based on facts gleaned from the foregoing criteria: (1) the fact that neither Finlay *et al.* nor Brashears *et al.* contain a teaching to suggest or motivate one of ordinary skill in the art to modify either reference or combine the reference teachings in order to arrive at the present invention; (2) the fact that neither Finlay *et al.* nor Brashears *et al.* can provide predictability of a reasonable expectation of success on administration of the claim-recited vaccine combination; and (3) the fact that all the claim limitations recited in the present application have not been taught or suggested by Finlay *et al.* and/or Brashears *et al.* In sum, the *prima facie* case of obviousness has not been established because the present invention, taken as a whole, is neither taught nor suggested by the art.

The basic elements of the method involve co-administering a vaccine composition which comprises inactivated or killed whole *E. coli* O157:H7, an antigen prepared from an O-specific polysaccharide of *E. coli* O157:H7 or a mixture thereof, and metabolizable oil adjuvant; and a *Lactobacillus acidophilus* or neomycin medicated feed supplement.

Examining what the collective art fairly teaches to the ordinary practitioner, it is clear that the practitioner would not arrive at the claimed invention since the combination of references does

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not teach or suggest all of the critical elements of the claimed invention. Neither the primary reference of Finlay *et al.* nor the secondary reference of Brashears *et al.* describe or imply that the whole bacterial cells can be used as a vaccine composition or that one could predict a reasonable degree of success on administration of the whole bacterin. Finlay *et al.* teach that cattle do not usually mount a significant serological response against the antigenic proteins following natural exposure to the organism and they advocate the use of the EHEC CCS that is substantially devoid of EHEC bacterial cells which, in effect, teaches away from the use of whole *E. coli* O157:H7 to elicit an immune reaction. There is no disclosure or suggestion of the value of using the bacterin in a vaccine. Finlay *et al.* actually discard the whole cells as worthless because they do not appreciate or suggest any benefit of using the whole bacterial cell. It is plain to see that the negative teachings of Finlay *et al.* would not motivate the ordinary practitioner to use the whole *E. coli* O157:H7, let alone combine it with the lactic acid bacteria of Brashears *et al.*

With respect to any suggestion of the fragments of *E. coli* O157:H7 being supplemented with *Lactobacillus acidophilus* per the Examiner's opinion, one reading Finlay *et al.* would appreciate and predict that the fragments could not be efficacious as a subunit vaccine. Rather, they would require the addition of the EHEC CCS that is substantially devoid of EHEC bacterial cells. Insofar as the teachings of the secondary reference are concerned, Brashears *et al.* suggest lactic acid bacteria such as *Lactobacillus acidophilus* might be a good candidate as a competitive exclusion product to inhibit or eliminate *E. coli* O157:H7. To put the two teachings together requires some idea seen in either Finlay *et al.* or Brashears *et al.* to suggest that combining probiotics with any bacterial vaccine would provide a reasonable expectation of success in further boosting an immune response or in reducing the shedding of *E. coli.* Such teaching is notably missing.

In fact, these references are being applied with the benefit of impermissible hindsight vision. Finlay *et al.* do not teach or suggest that their vaccine should or could be supplemented with lactic acid bacteria. Brashears *et al.* do not teach or suggest that their competitive exclusion product should or could be combined with a vaccine. The immune activity of a systemic bacterial vaccine has a very different mechanism of action than the exclusionary activity of the probiotics in the intestinal tract. In combination, there is absolutely no

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predictability of whether they would enhance or interfere with each other's diverse properties and modes of action.

To prove this last point, the Examiner's attention is respectfully drawn to the results of the study published by the National Cattlemen's Beef Association previously supplied to the Office. The fecal sample of the neomycin treated animals had no positive *E. coli* O157 isolates and the vaccine treated animals had a prevalence of 14.7% positive isolates yet when neomycin was combined with the vaccine, the fecal sample showed an increased prevalence of 26.7%. While there was an improvement seen in the hide percentages of the combined intervention over each one alone, the poor results of the fecal samples show that one cannot expect success from the combinations without testing them. The need for further experimentation obviates any contention of obviousness to make the combination.

Moreover, there is nothing in the art to suggest the use of the probiotic with the vaccine composition comprising inactivated or killed whole *E. coli* O157:H7, the antigen prepared from an O-specific polysaccharide of *E. coli* O157:H7 or the mixture thereof in combination with the metabolizable oil adjuvant taught in the specification. Over 60 years ago, alum-adsorbed allergen extracts were first used for depot vaccination and since that time, aluminum hydroxide continues to be the most common adjuvant in vaccines. It is noted that even the reference WO 00/04922 solely describes the conventional aluminum hydroxide adjuvant and suggests no other adjuvant for use with the antigen prepared from an O-specific polysaccharide of *E. coli* O157:H7.

Applicants took a different approach from the art and included the unique metabolizable oil adjuvant in their vaccine composition with beneficial and unexpected results over those seen in the prior vaccines. In the working Example 2 set forth in the application, Applicants compare the art-recognized aluminum hydroxide as the standard vehicle in the vaccine of Group 6 and show significant improvement when the metabolizable SP oil taught in the specification is added to the aluminum hydroxide adjuvanted formulation (Group 7). Quite unexpectedly, the vaccine composition of the invention in Group 7 demonstrated the greatest overall serological titers and the best improvements in immunity; and, equally surprising under the circumstances, the animals displayed minimal, normal reactions at the vaccine administration sites.

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The reaction scores show that the vaccine of the invention is unpredictably safe on administration. With all vaccinations, a little lump is expected when the active ingredient is released slowly from the site of depot administration. However, it is typical for vaccines that give a higher immune response to cause a greater reaction. Because a severe lump usually forms from vaccines with significantly higher immunogenic responses, it was initially thought that the claimed vaccine composition would cause a greater adverse reaction. Surprisingly, the numbers were close on comparison and no major reaction had been observed. Despite the higher immune response, the results demonstrated that the size of the reaction lump was the same as the traditional vaccine and, unexpectedly, no safety issue was found.

All in all, the above showing of the references' flaws and the objective evidence of superior activity of the vaccine composition of the present invention sufficiently refute the holding of obviousness. Thus, in view of the proffered amendment and the foregoing remarks, it is respectfully asked that the rejection of Claim 23 under 35 U.S.C. § 103(a) be withdrawn.

Accordingly, it is believed that this application is now in condition for an allowance. Favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

Date: February 10, 2006

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APPENDIX

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows:

Claims 1-21 (Canceled).

Please add new Claims 22 and 23 as follows:

Claim 22 (New): A method for reducing shedding of *E. coli* O157:H7 in an animal which comprises administering to the animal a vaccine composition which comprises an immunogenically active component comprising inactivated or killed whole *E. coli* O157:H7, an antigen prepared from an O-specific polysaccharide of *E. coli* O157:H7 or a mixture thereof; a metabolizable oil adjuvant; and optionally a pharmaceutically acceptable carrier.

Claim 23 (New): The method according to Claim 22 which further comprises administering a *Lactobacillus acidophilus* or neomycin medicated feed supplement to the animal.